Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Cluster headache and other trigemino-autonomic cephalgias.

Bibliographic Source(s)

Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sandor PS. Cluster headache and other trigemino-autonomic cephalgias. In: Gilhus NE, Barnes MP, Brainin M, editor(s). European handbook of neurological management. 2nd ed. Vol. 1. Oxford (UK): Wiley-Blackwell; 2011. p. 179-90. [141 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: May A, Leone M, Afra J, Linde M, Sandor PS, Evers S, Goadsby PJ, EFNS Task Force. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. Eur J Neurol 2006 Oct;13(10):1066-77.

Recommendations

Major Recommendations

The levels of evidence (Class I-IV) supporting the recommendations and ratings of recommendations (A-C) are defined at the end of the "Major Recommendations" field.

Treatment Recommendations for Cluster Headache, Paroxysmal Hemicrania and Short-lasting Unilateral Neuralgiform Headache Attacks with Conjunctival Injection and Tearing (SUNCT) Syndrome

	Treatment of Choice		
Therapy	Cluster Headache	Paroxysmal Hemicrania	SUNCT Syndrome
Attack treatment	Oxygen inhalation (A) Sumatriptan 6 mg, sc (A) Zolmitriptan 5 mg nasal (A) Sumatriptan 20 mg nasal (A) Zolmitriptan 10 mg oral (B) Lidocaine nasal (B) Octreotide (B)	None	None

Treatment of Choice			
Prophylactic treatment	Verapamil (A) Steroids (A) Lithium (B)	Indomethacin (A) Verapamil (C) NSAIDs (C)	Lamotrigine (C)
Therapy	Cluster Headache	Paroxysmal Hemicrania	SUNCT Syndrome
	Methysergide (B) Topiramate (B) Ergotamine tartrate (B) Valproic acid (C) Melatonin (C) Baclofen (C)	Topiramate (C)	

NSAIDs = non-steroidal anti-inflammatory drugs; sc = subcutaneous

For exact doses see text of the original guideline document (A denotes effective, B denotes probably effective, C denotes possibly effective).

Treatment of Cluster Headache

Level A Recommendations

As first choice, acute attacks of cluster headache should be treated with the inhalation of 100% oxygen with at least 7 l/min over 15 min (Class II trials) or with the subcutaneous injection of 6 mg sumatriptan or the intranasal application of zolmitriptan 5 mg (Class I trials). As second choice, sumatriptan 20 mg nasal spray can be used (Class I trial) with minor efficacy or more side effects.

Prophylaxis of cluster headache should be first tried with verapamil in a daily dose of at least 240 mg (maximum dose depends on efficacy or tolerability; electrocardiogram [ECG] controls are obligatory with increasing doses). Although no Class I or II trials are available, steroids are clearly effective in cluster headache. Therefore, the use of at least 100 mg oral up to 500 mg intravenous (i.v.) per day methylprednisone (or equivalent corticosteroid) over 5 days (then tapering down) is recommended.

Level B Recommendations

Intranasal lidocaine (4%) can be tried in acute cluster headache attacks if Level A medication is ineffective or contraindicated. Oral zolmitriptan 10 mg is effective in some patients (Class I trial) but high dose produces many side effects and limits practical use.

Methysergide and lithium are drugs of second choice if verapamil is ineffective or contraindicated. Corticosteroids can be used for short courses where bouts are short or to help establish another medicine. Topiramate is promising, but only open trials exist at this point. Melatonin is useful in some patients. Except for lithium, the maximum dose depends on efficacy and tolerability. Ergotamine tartrate is recommended for short-term prophylaxis (Class III studies). In spite of positive Class II studies, pizotifen and intranasal capsaicin should not be used because of side effects.

Level C Recommendations

Baclofen 15 to 30 mg and valproic acid showed possible efficacy and can be tried as drugs of third choice.

Surgical procedures are not indicated in most patients with cluster headache. Patients with intractable chronic cluster headache should be referred to centres with expertise in both destructive and neuromodulatory procedures to be offered all reasonable alternatives before a definitive procedure is conducted.

Treatment of Paroxysmal Hemicrania

Paroxysmal hemicrania is to be treated with indomethacin up to 200 mg (Level A recommendation). Alternatively, verapamil, topiramate, and different nonsteroidal anti-inflammatory drugs (NSAIDs) can be tried (Level C recommendation).

Treatment of Short-lasting Unilateral Neuralgiform Headache Attacks with Conjunctival Injection and Tearing (SUNCT) Syndrome

No recommendation can be given for the treatment of SUNCT syndrome. Treatment with lamotrigine (at least 100 mg) is considered the first-line option.

Definitions:

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population

or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Rating of Recommendations

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Cluster headache
Paroxysmal hemicrania
Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome

Guideline Category

Assessment of Therapeutic Effectiveness

Management

Prevention

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Neurology

Pharmacology

Preventive Medicine

Intended Users

Physicians

Guideline Objective(s)

To give evidence-based recommendations for the treatment of cluster headache attacks, for the prophylaxis of cluster headache, for the treatment of paroxysmal hemicranias, and for the treatment of short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome

Target Population

Patients suffering from cluster headache, paroxysmal hemicranias, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome

Interventions and Practices Considered

Treatment

Cluster Headaches

1. 100% oxygen
2. Triptans (e.g., sumatriptan, zolmitriptan)
3. Intranasal lidocaine
4. Subcutaneous octreotide

Paroxysmal Hemicrania

1. Indomethacin
2. Verapamil
3. Non-steroidal anti-inflammatory drugs (NSAIDs)
4. Topiramate

Note: The following were considered but not recommended for treatment of short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome: lamotrigine, gabapentin, topiramate, oxcarbazepine, verapamil, intravenous lidocaine, steroids, intravenous phenytoin, and stimulation of the hypothalamus. Lamotrigine is considered first-line treatment.

Prevention

Cluster Headaches

1. Verapamil
2. Steroids
3. Lithium carbonate
4. Methysergide
5. Topiramate
6. Ergotamine tartrate
7. Valproic acid
8. Melatonin

9. Baclofen

Major Outcomes Considered

Effectiveness of treatment
Prevention of attacks

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A literature search was performed using the reference databases Medline, Science Citation Index and the Cochrane Library; the keywords used were 'cluster headache', 'paroxysmal hemicrania', 'SUNCT', 'treatment' and 'trial' (last search in March 2009). All papers published in English, German or French were considered when they described a controlled trial or a case series on the treatment of at least five patients (or fewer in paroxysmal hemicrania or short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing [SUNCT] syndrome). In addition, a review book and the German treatment recommendations for cluster headache were considered.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

All authors performed an independent literature search. The first draft of the manuscript was written by the chairman of the task force. All other members of the task force read the first draft and discussed changes by email. A second draft was then written by the chairman and was again discussed by email. All recommendations had to be agreed to by all members of the task force unanimously. The background of the research strategy and of reaching consensus and the definitions of the recommendation levels used in this paper have been described in the European Federation of Neurological Societies (EFNS) recommendations (see the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Rating of Recommendations

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see the "Availability of Companion Documents" field).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendations (see the "Major Recommendations" field).

The recommendations are based on the scientific evidence from clinical trials and on the expert consensus by this European Federation of Neurological Societies task force.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment of cluster headache, paroxysmal hemicranias, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome

Potential Harms

- The most unpleasant side effects of *sumatriptan* are chest pain and distal paraesthesia.
- Oral *zolmitriptan* 10 mg produces many side effects and limits practical use.
- Side effects of *verapamil* are bradycardia, oedema, constipation, gastrointestinal discomfort, gingival hyperplasia, and dull headache. Regular electrocardiographic (ECG) controls are required to control for an increase in cardiac conduction time. Sometimes, echocardiography can be necessary due to the negative inotropic effects of verapamil.
- Major side effects of *lithium* are hypothyroidosis, tremor, and renal dysfunction. Lithium should be monitored by the plasma level which should be between 0.3 and 1.2 mmol/l. Regular control of liver, renal and thyroid function and of electrolytes is required.
- Since there is small but important incidence of pulmonary and retroperitoneal fibrosis, the continuous use of *methysergide* is limited to a maximum of 6 months.
- Main side effects of *topiramate* and *gabapentin* are cognitive disturbances, paraesthesias, and weight loss.
- Gastrointestinal discomfort and bleedings are the major side effects of *indomethacin*. Therefore, a proton pump inhibitor should be given in addition.
- High morbidity from *corticosteroids* suggests caution, short courses, and avoidance in chronic cluster headache.
- In cluster headache patients, a risk for the development of medication overuse headache has been shown, in particular if there is a comorbidity or a family history of migraine.

Contraindications

Contraindications

- Contraindications to sumatriptan are cardio- and cerebrovascular disorders and untreated arterial hypertension.
- Topiramate is contraindicated in nephrolithiasis.
- Major contraindication to indomethacin is a gastrointestinal disorder.

Qualifying Statements

Qualifying Statements

- This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.
- The recommendations are based on the scientific evidence from clinical trials and on the expert consensus by this EFNS task force. The legal aspects of drug prescription and drug availability in the different European countries will not be considered.

Implementation of the Guideline

Description of Implementation Strategy

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2006 Oct (revised 2011)

Guideline Developer(s)

European Academy of Neurology - Medical Specialty Society

Source(s) of Funding

European Federation of Neurological Societies

Guideline Committee

European Federation of Neurological Societies Task Force on Cluster Headache and Other Trigemino-Autonomic Cephalgias

Composition of Group That Authored the Guideline

Task Force Members: S. Evers, University of Münster, Germany; J. Áfra, National Institute of Neurosurgery, Budapest, Hungary; A. Frese, University of Münster, Germany and Academy of Manual Medicine, Münster, Germany; P. J. Goadsby, University of California, San Francisco, CA, USA and UCL, Institute of Neurology, Queen Square, London, UK; M. Linde, Cephalea Headache Centre, Läkarhuset Södra vägen, Gothenburg, Sweden; A. May, University of Hamburg, Germany; P. S. Sándor, University of Zurich, Switzerland

Financial Disclosures/Conflicts of Interest

The present guidelines were developed without external financial support. The authors report the following financial supports:

Stefan Evers: Salary by the University of Münster; honoraries and research grants by Addex Pharm, AGA Medical, Allergan, Almirall, AstraZeneca, Berlin Chemie, Boehringer, CoLucid, Desitin, Eisai, GlaxoSmithKline, Ipsen Pharma, Janssen Cilag, MSD, Novartis, Pfizer, Pharm Allergan, Pierre Fabre, Reckitt-Benckiser, UCB.

Judit Áfra: Salary by the Hungarian Ministry of Health.

Achim Frese: Private praxis; honorary by Berlin Chemie.

Peter J. Goadsby: Salary from University of California, San Francisco; honorarium or research grants in 2008 from Almirall, Boston Scientific, Colucid, Eli Lilly, GSK, J & J, MAP Pharmaceuticals, MSD, Medtronic, Neuralieve.

Mattias Linde: Salary by the Swedish government; honoraries by AstraZeneca, GlaxoSmithKline, MSD, Nycomed, Pfizer.

Arne May: Salary by the University Hospital of Hamburg; honoraries by Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, GlaxoSmithKline, Janssen Cilag, MSD, Pfizer.

Peter S. Sándor: Salary by the University Hospital of Zurich; honoraries by AstraZeneca, GlaxoSmithKline, Janssen Cilag, Pfizer, Pharm Allergan.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies (EFNS) Web site .

Availability of Companion Documents

The following is available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on April 11, 2007. The information was verified by the guideline developer on May 15, 2007. This summary was updated by ECRI Institute on May 1, 2009 following the U.S. Food and Drug Administration advisory on antiepileptic drugs. This summary was updated by ECRI Institute on January 8, 2010 following the U.S. Food and Drug Administration advisory on Valproate sodium. This summary was updated by ECRI Institute on July 26, 2010 following the U.S. Food and Drug Administration (FDA) advisory on Proton Pump Inhibitors (PPI). This summary was updated by ECRI Institute on September 15, 2010 following the U.S. Food and Drug Administration advisory on Lamictal (lamotrigine). This summary was updated by ECRI Institute on April 13, 2011 following the U.S. Food and Drug Administration advisory on Topamax (topiramate). This summary was updated by ECRI Institute on February 20, 2012. This summary was updated by ECRI Institute on July 10, 2013 following the U.S. Food and Drug Administration advisory on Valproate. This summary was updated by ECRI Institute on September 18, 2015 following the U.S. Food and Drug Administration advisory on non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs).

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